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# Coarse-Grained Simulations of Protein Adsorption on Solid Surfaces

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The adsorption of proteins on solids and soft materials plays a vital role in biotechnical and biomedical applications, for example for the biocompatibility of implant material or in dental health care. Not only the properties of the sorbent surface can be changed, but also the proteins might undergo conformational changes during adsorption. To investigate such processes in molecular detail, but still reaching appropriate time scales (microseconds), coarse-grained molecular dynamics simulations were applied here. As a model system, the adsorption of lysozyme and human serum albumin to a simple, slightly negatively charged, single-layer solid surface were studied at various ion concentrations. Adsorption rates of the two proteins, protein diffusion before and after attachment to the surface, and the orientation of the proteins on the surface were analyzed.

## 1 Introduction

The modeling of protein adsorption is challenging, because even the single protein dynamics takes place on timescales that are hardly accessible within atomistic simulations. Therefore it is necessary to use coarse-grained models, which describe only partially the internal degrees of freedom of the proteins and the surrounding solution. While the limitations of all-atom simulations are of the order of 10 nm in space and 100 ns in time, they can be extended to the microsecond timescale by the application of a coarse-grained (CG) simulation scheme. In CG simulations, small groups of atoms are treated as single particles, thus reducing the total number of simulated degrees of freedom. Additionally, the larger objects allow for a 10- to 20-fold increase of the time step for integration (from 2 fs to 20–40 fs); also, the absolute dynamics in CG systems is increased by a factor of 4 with respect to real systems<sup>1</sup>. In total, the accessible simulation time of medium-sized systems is thereby increased to the submillisecond timescale. Recently, the CG approach has e.g. successfully been applied to study the assembly of transmembrane proteins into lipid bilayers or the self-assembly of high-density lipoproteins.

## 2 Methods

Coarse-grained simulations on the microsecond time scale were employed to study the aggregation of individual proteins on a negatively charged surface mimicking a mica surface, as well as the lateral protein diffusion. Proteins and water molecules were modeled in the recently developed MARTINI force field<sup>1,2</sup>, with additional constraints on the protein to

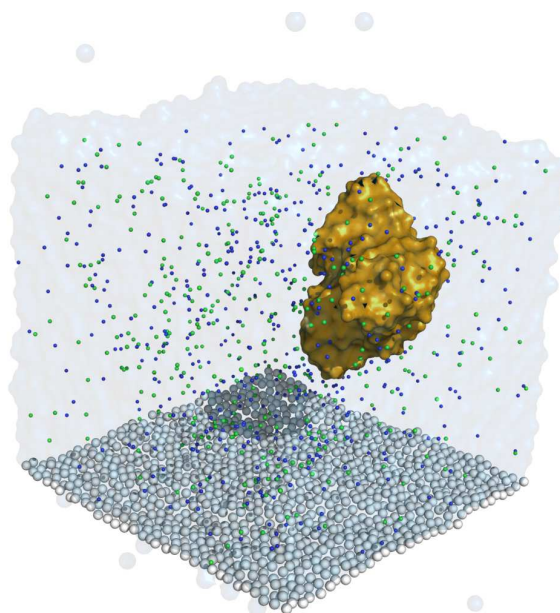


Figure 1. Simulation system for the aggregation study of human serum albumine (HSA, orange) on a solid surface (grey spheres) in explicit ionic solution (0.2 M NaCl, green and blue spheres). The box dimensions are approximately 15 nm in all directions, the total number of cg atoms is approximately 26,000. Aggregation times of HSA to the mica surface range between 1 and 10  $\mu$ s. Initially, HSA is randomly placed in the water box.

preserve the overall secondary and tertiary structure. Initially, the proteins were randomly placed into the water box (Fig. 1).

### 3 Results

Typical aggregation times determined from the coarse-grained MD simulations range from 1  $\mu$ s for lysozyme to about 5  $\mu$ s for human serum albumine, reflecting the different sizes and therefore different diffusion coefficients of the investigated proteins (164 vs. 585 residues). While these time- and length scales (the cg system for human serum albumine corresponds to an all-atom system size of roughly 350,000 atoms) are inaccessible by all-atom simulations, coarse-grained simulations even allow to obtain sufficient statistics on the aggregation process: From in total 27 aggregation simulations of lysozyme on the surface (duration of each run 4  $\mu$ s) contact patterns of surface amino acids with the solid surface could be determined (see Fig. 2). These clearly show preferred orientations of lysozyme on the surface.

### 4 Discussion

Protein aggregation on modeled surfaces has been shown to be accessible by a coarse-grained simulation scheme, thereby opening the lane towards atomic-scale studies on the formation of biofilms. Protein diffusion is drastically reduced on the surface, however,

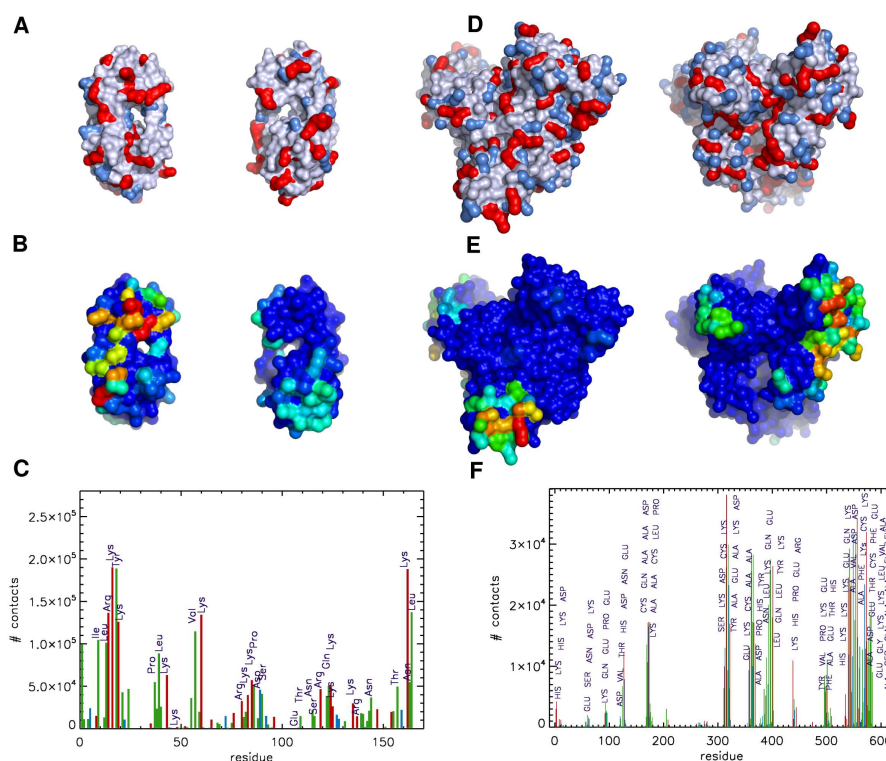


Figure 2. All-atom representation of lysozyme (A) and of HSA (B) with residues colored according to their net charge (red +1, blue -1). Additionally, the coarse-grained proteins (B and E) are shown with color-coded interaction frequencies (C and F) to the negatively charged surface (red high frequency; blue no contacts).

still present. Next steps include partial freeing of the introduced elastic constraints on the protein to allow for large-scale conformational changes and/or unfolding.

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